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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/713,546	11/14/2003	Hans E. J. Hofland	020681-001710US	7974

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1615	

MAIL DATE	DELIVERY MODE
08/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/713,546	HOFLAND, HANS E. J.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date: _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment dated 7-12-07 is acknowledged.

Claims included in the prosecution are 8-11.

In view of the amendments to the claims, the 112, 102 rejections are withdrawn.

Claim Rejections - 35 USC § 103

1. Claims 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cavazza (5,747,536) in view of Keller (6,726,924) or Foldvari (5,993,851) individually or in combination.

Cavazza teaches the effectiveness of L-carnitine and its esters in the treatment of peripheral vascular diseases. The derivatives taught by Cavazza are acetyl L-carnitine and propionyl L-carnitine (abstract, columns 3-5 and claims).

What is lacking in Cavazza is the use of liposomes as the delivery vehicles for carnitines.

Keller discloses that liposomes are sustained release delivery vehicles for a variety of active agents including L-carnitine. According to Keller, liposomes increase the bioavailability of active agents when administered (col. 2, lines 13-65).

Foldvari while disclosing liposomal formulations containing various biologically active agents for topical delivery teaches that several studies showed that liposome encapsulation advantageously alters the pharmacokinetic fate of the drug after topical application (abstract, col. 1, lines 49-52) and that liposomes (containing active agent, PGE1) can be used to treat diseases including peripheral vascular disease (col. 27, lines 41-47).

The use of liposomes as the delivery vehicles for the compositions of Brevetti would have been obvious to one of ordinary skill in the art since Keller teaches that liposomes are sustained release delivery vehicles and increase the bioavailability of active agents and Foldvari teaches that the topical delivery of liposomes can be used to treat peripheral vascular diseases. Alternately to use liposomes for the encapsulation of L-carnitine or its esters for treatment of peripheral vascular diseases would have been obvious to one of ordinary skill in the art since L-carnitine and its esters are effective against this disease as taught by Brevetti. One of ordinary skill in the art would expect the advantages of liposomes in the delivery of L-carnitine.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that Cavazza actually teaches away from the use of a pharmaceutical composition comprising alkyl-L-carnitine alone as the active agent for the treatment of peripheral arterial disease as presently claimed. Applicant further argues the following. "Cavazza describes that the pathological basis of cardiovascular diseases, peripheral vascular diseases and diabetic peripheral neuropathy is undesired platelet aggregation. Cavazza performed *in vitro* platelet aggregation tests to quantify the inhibitory effects of, *inter alia,* L-carnitine alone, resveratrol alone (a trihydroxy-stilbene), and combination thereof on platelet aggregation and used these results to evaluate the potential effectiveness of these compounds for treating various disease, including cardiovascular diseases, peripheral vascular diseases, and diabetic peripheral neuropathy. In short, Cavazza discloses that L-carnitine, when used by itself, was *completely ineffective* at inhibiting platelet aggregation. The disclosure of Cavazza would clearly suggest to a

skilled artisan that a composition comprising L-carnitine alone *is not* effective at treating the aforementioned diseases since Cavazza clearly teaches that L-carnitine (or derivatives thereof) alone does not inhibit platelet aggregation. Specifically, Cavazza teaches at column 4, lines 51- 62."

These arguments are not found to be persuasive. First of all, instant claim language does not exclude other components taught by Cavazza and Cavazza teaches 100 % inhibition of platelet aggregation of the carnitine esters and resveratrol (col. 5, line 1 et seq.). Secondly, Cavazza' teachings are not based on platelet aggregation alone. On col. 3, lines 50-56, Cavazza teaches that L-carnitine and particularly propionyl L-carnitine can act by varying the lipid substrate from which come, as a result of the action of cyclooxygenases and lipo-oxygenases, the various vasoconstricting and pro-aggregation factors, reducing their formation and facilitating the synthesis of anti-aggregating and vasodialatory factors. Synergism means that each component has some effect and when combined, the effect is more than additive. Instant application does not contain any data to show that claimed compounds have any effect on claimed disease condition. Applicant's arugments that Keller is directed to oral liposomal delivery system, but does not teach claimed alkyl-carnitine are not persuasive since instant claims do not recite the mode of administration and since Keller is combined to show that liposomes increase the bioavailability of the administered compounds which include carnitine and one would expect the increase in bioavailability of any compound including the derivatives of carnitine. One of ordinary skill in the art would be motivated

to encapsulate instant compounds based on Foldvari, which teaches liposomal administration of active agents for the treatment of peripheral arterial diseases.

2. Claims 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brevetti (4,968,719) in view of Keller (6,726,924) or Foldvari (5,993,851) individually or in combination, further in view of Cavazza cited above.

Brevetti teaches L-carnitine's effectiveness for the treatment of peripheral vascular diseases (abstract, Examples and claims).

What is lacking in Brevetti is the use of liposomes as the delivery vehicles for Carnitine and the use of claimed derivatives of carnitinel.

Keller discloses that liposomes are sustained release delivery vehicles for a variety of active agents including L-carnitine. According to Keller, liposomes increase the bioavailability of active agents when administered (col. 2, lines 13-65).

Foldvari while disclosing liposomal formulations containing various biologically active agents for topical delivery teaches that several studies showed that liposome encapsulation advantageously alters the pharmacokinetic fate of the drug after topical application (abstract, col. 1, lines 49-52) and that liposomes (containing active agent, PGE1) can be used to treat diseases including peripheral vascular disease (col. 27, lines 41-47).

Cavazza as pointed out above, teaches the effectiveness of L-carnitine and its esters in the treatment of peripheral vascular diseases. The derivatives taught by Cavazza are acetyl L-carnitine and propionyl L-carnitine (abstract, columns 3-5 and claims).

The use of liposomes as the delivery vehicles for the compositions of Brevetti would have been obvious to one of ordinary skill in the art since Keller teaches that liposomes are sustained release delivery vehicles and increase the bioavailability of active agents and Foldvari teaches that the topical delivery of liposomes can be used to treat peripheral vascular diseases. The use of the claimed derivatives of carnitine would have been obvious to one of ordinary skill in the art since Cavazza teaches the use of these derivatives for the treatment of the same disease.

2. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is

(571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Woodward Michael can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK